REMARKS

THE PENDING CLAIMS ARE NOT OBVIOUS IN VIEW OF THE CITED ART

The Examiner has rejected claims 1-14 as being allegedly obvious over Uchida et al. (U.S. 6,150,092) in view of Robinson (WO 95/04142), Agrawal et al. (PNAS 4: 2620-2625, 1997) and Bennett et al. (U.S. 5,998,148).

The Examiner argues that, "The antisense oligonucleotides claimed by Uchida et al. are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO:7. It is noted that antisense oligonucleotides of the instant application, including claimed SEQ ID NO:34 (modified version of SEQ ID NO:2) as well as SEQ ID NOS: 2, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 28 and 29, for example, are all targeted to SEQ ID NO:7 of Uchida et al., and further all the antisense oligonucleotides of the instant application either overlap, embrace or are embraced by the specifically claimed antisense of Uchida et al."

The Examiner concedes that Uchida et al. does not disclose the 2' O-methyl modifications of SEQ ID NO:34, the specific cells of claim 7, combinations with chemotherapeutic agents or the use of liposomes. However the Examiner suggests that the 2' O-methyl modifications are disclosed by Robinson et al., and that Agrawal et al. have taught the same modification used in SEQ ID NO:34, in Table 1, for example. The Examiner states, "It has been taught that this oligonucleotide has nuclease resistance, for example." The Examiner further suggests that Bennett et al. teaches many modifications as well as liposome delivery.

Applicants respectfully assert that the claims are not obvious in view of the cited art. All of the claims are drawn to or include the oligonucleotide of SEQ ID NO:34, and Applicants maintain, for reasons described below, that this oligonucleotide is not obvious in view of the cited art. Accordingly, none of the pending claims are obvious.

In order to make out a *prima facie* case of obviousness, the Examiner must show not only that the elements of the claim could have been picked out of the forest of available art, but that

there was reason to motivate one of ordinary skill in the art to do so. The courts have cautioned against the use of an applicant's disclosure itself as a road map for piecing together the components of an invention from a set of references without any apparent motivation in the art to do so. See for example, *In re Napier,* 55 F.3d 610, 613 (Fed. Cir. 1995), "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." See also *In re Laskowqski*, 871 F.2d 115, 117 (Fed. Cir. 1989), "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." Applicants assert that the Examiner has failed to show that one of ordinary skill in the art would be motivated to combine the cited references in such a way as to arrive at the nucleic acid of SEQ ID NO:34.

Uchida et al.

Turning first to Uchida: this reference does not encompass or overlap all of the oligonucleotides presented in the present application, and the predictive value of Uchida as a whole is highly questionable. In addition, all of the oligonucleotides are not at issue in the presented claims, and Applicants respectfully request that, in the interest of an efficient prosecution, the Examiner limit his comments to the claimed subject matter and refrain from *ad hoc* comments on the patentability of unclaimed embodiments.

As acknowledged by the Examiner, Uchida neither discloses the exact modified nucleic acid of SEQ ID NO:34 nor the related, unmodified form presented in SEQ ID NO:2. Instead, the Examiner suggests that one of ordinary skill in the art would view Uchida as a reliable guide to certain portions of the VEGF gene that are desirable targets for antisense oligonucleotides. In particular, the Examiner points to the Uchida's SEQ ID NO:7 as a region that is allegedly desirable to target. Applicants' SEQ ID NO:2 does in fact have a sequence that falls within the region defined by Uchida's SEQ ID NO:7. Nonetheless, one of ordinary skill in the art would not recognize Uchida's "regions" as having any meaningful predictive value. In Table 1, Uchida shows an experiment in which 80 antisense probes with a uniform length of 20 unmodified nucleotides were tested for effectiveness in an in vitro (cell-free) assay. Of these 80 probes, only 14 failed to show an activity that was not termed either "strong" or "very strong" by Uchida et al.

Although Uchida et al. interpret the 66 effective probes as defining desirable portions of the VEGF sequence to target, Applicants assert that, most likely, the 14 failed probes were merely random occurrences, scattered along the VEGF sequence with no correlation to any particularly suitable or unsuitable regions to target for antisense. Many factors were known to influence the effectiveness of antisense probes, in addition to position within a gene, and Uchida did not control for these variables. As taught by Agrawal et al. at page 2622, "Thermodynamic stability of an oligo to the target RNA and activation of RNAse H are important parameters for its antisense activity." Uchida et al did include some added exogenous RNase H in the assay system, so the differences between probes may have more to do with RNase activation than any particular location in the VEGF gene. In addition, Applicants note that there is an odd and perhaps not coincidental bias in the GC content of the 80 probes that were used. Among the 14 failed probes, the average GC content was 12.57 GC nucleotides out of 20 (63% GC), while among the 66 successful probes, the average GC content was 10.20 GC nucleotides out of 20 (51% GC) (Applicants have double-checked this laborious calculation, but welcome further checking by the Examiner). It is well-known that GC percentage increases thermodynamic stability of hybridized nucleic acid duplexes. Uchida et al. therefore failed to control for a fundamental variable in antisense effectiveness, and it seems likely that the 14 failed probes failed because of issues to do with the composition of the probes and not any particular sequence or position in VEGF. It appears that the real teaching of Uchida et al. may be that, for VEGF antisense, one should select probes having low GC content. Applicants concede that SEQ ID NO:2 and 34 have relatively low GC content, however, a teaching of a desirable range of GC content is not by any means a teaching of a particular probe sequence. Oddly, Agrawal et al. teach that a higher thermostability (e.g., by higher GC content) is actually desirable, so it is unclear what the combined teachings of Agrawal and Uchida convey to one of ordinary skill in the art. It is interesting to note that the Uchida assay is an in vitro, cell free assay, and it may be that this assay produces somewhat aberrant results. This hypothesis is supported by Uchida's few cell-based assays, presented in Table 9. In Table 9, Uchida et al. tested three 20mer phosphorothioate modified probes that were highly effective in the cell-free assay (NO. 37 showed roughly 20-fold greater suppression than controls, NO. 47 showed roughly 60-fold greater suppression, and NO. 51 showed roughly 15-fold greater suppression, assuming an average control probe value of 0.6). The phosphorothioate modified versions, in the cell based

assays, showed only about 1.3 fold, 1.5 fold and 1.4 fold improvement over controls, respectively (assuming a control probe value of 0.9), and this even when the controls themselves had far less effect on expression than in the cell-free system. Therefore, one of ordinary skill in the art would have considerable reason to suspect that Uchida's cell-free assay was nearly worthless as a predictor of probe effectiveness in a cellular setting. Notably, both SEQ ID NO: 51 and 47 derive from the so-called desirable target region of Uchida's SEQ ID NO:7.

Applicants note that obviousness is to be assessed from the point of view of one of ordinary skill in the art. Applicants submit that the skill level in the field of antisense is quite high. In fact, the Court of Appeals for the Federal Circuit has had the occasion to assess the level of skill in the field of antisense technology, and the court determined that one of ordinary skill in the art would be a post-doctoral researcher. *Enzo Biochem Inc. v. Calgene Inc.*, 52 USPQ2d 1129 at 1137 (Fed. Cir. 1999). Such a person would be well able to grasp the above-described shortcomings in Uchida. In fact, the failure to control for possible confounding variables is a fundamental flaw in experimental design.

To conclude, one of ordinary skill in the art would appreciate that Uchida et al. provides no meaningful guidance for antisense probe selection. Even if one accepts the predictions regarding regions in the in vitro assays (which there is substantial reason to doubt), it does not appear that these predictions transfer to the cellular setting or to phosphorothioate modified probes. Therefore, one of skill in the art would not be able to discern any particular variants to be made on the basis of Uchida. Given that SEQ ID NO:2 and SEQ ID NO:34 are not disclosed literally in Uchida, it is unreasonable to assume that one of ordinary skill in the art could find in the teachings of Uchida any motivation to make those particular sequences. In addition, no other reference cited provides any sequence that is similar to those of SEQ ID NO:2 or SEQ ID NO:34.

Agrawal, Robinson and Bennett

With respect to Agrawal et al., the Examiner suggests that this references teaches the desirability of an antisense oligonucleotide comprising four 2' O-methyl modifications at the 5' and 3' ends. It is true that Agrawal tests a probe having such modifications (probe 9, table 1; this probe has no sequence similarity to SEQ ID NOs 2 or 34 of the instant application), but Agrawal

actually teaches away from the use of this modification. In the Abstract, Agrawal reads, "Some of these MBOs indicate improved properties compared with phosphorothioate oligodeoxynucleotides with respect to affinity to RNA, RNAse H activation, and anti-HIV activity. As noted above, Agrawal states at page 2622, first sentence of the "Results", "[A]ctivation of RNase H [is an] important parameter for its antisense activity." At the bottom of the first column of page 2622, Agrawal reports, "[RNase H] Cleavage of RNA in the presence of centrally modified MBOs (oligos 2-8 and 12-14) was faster than cleavage in the present of PS-oligo or end-modified MBOs (Table 1)." In Table 1, it can be seen that oligonucleotide 9 had the slowest activation of RNase H of any of the 16 probes tested. It is perhaps for this reason that Agrawal et al. did not even bother to test probe 9 in any of the HIV or other cell-based assays. Accordingly, Agrawal et al. teaches away from the use of end-modified oligonucleotides because these appear to have a slower activation of RNase H. Applicants note that the activation of RNase H is desirable, according to Agrawal, while susceptibility to nucleases generally is undesirable.

With respect to Robinson et al., this reference speaks only generally about the desirability of using various modifications, and does not suggest the particular combination of modifications present in SEQ ID NO:34 nor the positioning of the 2' O-methyl modifications.

Bennett et al. does not appear to correct any of the defects in the other art.

So, to conclude, there is no teaching, suggestion or motivation for making the particular sequence of either SEQ ID NO:2 or SEQ ID NO:34 in Uchida et al. Agrawal et al. actually teaches away from the modifications that are present in SEQ ID NO:34, and none of the other references cited by the Examiner repair these defects. Accordingly, the Examiner has failed to make a *prima facie* case of obviousness against claim 1 or any of the claims depending therefrom. The same is true, for the same reasons, with respect to independent claim 9 and the claims depending therefrom.

Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

Applicants respectfully disagree with the Examiner regarding the application of inherency to the pending claims, however, it is Applicants' belief that the point is moot in view of the foregoing arguments.

IV. CONCLUSION

In view of the foregoing remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants hereby request that any fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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